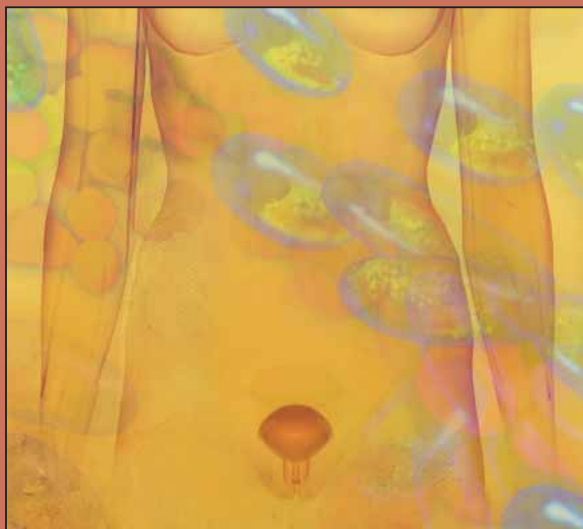


Managing Acute Uncomplicated Cystitis in Women in the Era of Antibiotic Resistance: A Case-Based Approach to the Pregnant Woman and the Pediatric Population

The second in a series of educational newsletters



PRESENTED BY

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Therapy	Off-Label Use
Fluoroquinolones	Use in pediatric/pregnant patients
Fosfomycin	Pregnant patients
All UTI therapies	Prophylaxis

TARGET AUDIENCE

Urologists, obstetricians/gynecologists, pediatricians, primary care physicians (general practitioners, family practitioners, internal medicine physicians) and other healthcare professionals who care for patients with acute uncomplicated cystitis.



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MANAGING ACUTE UNCOMPLICATED CYSTITIS IN WOMEN IN THE ERA OF ANTIBIOTIC RESISTANCE: A CASE-BASED APPROACH TO THE PREGNANT WOMAN AND THE PEDIATRIC POPULATION

INTRODUCTION

This is the second in a series of newsletters based in part on presentations from an August 2002 scientific roundtable presented by The Office on Women's Health of the U.S. Department of Health and Human Services and jointly sponsored by the University of Washington School of Medicine and IMED Communications entitled *Managing Acute Cystitis in Women in the Era of Antibiotic Resistance*. The goal of the roundtable was to examine the impact of antibiotic resistance on the management of acute uncomplicated urinary tract infection (cystitis) in women. This newsletter examines the diagnosis and management of urinary tract infection (UTI) in pregnant and pediatric patients.

Acute uncomplicated cystitis (AUC), or urinary tract infection (UTI) is a symptomatic infection of the bladder, or lower urinary tract, that occurs in a patient with a normal genitourinary tract.^{1,2} Diagnosis of AUC is usually based upon clinical presentation and rarely requires laboratory evaluation.^{1,2} Asymptomatic bacteriuria (ASB) is the presence of significant bacteria ($>10^5$ col/mL) in the absence of symptoms.³ Treatment of cystitis among healthy women traditionally uses empiric antibiotic therapy of 3 or 7 days⁴ and long-term medical sequelae of AUC in otherwise healthy adults are rare. UTIs occurring among pregnant or pediatric patients may have additional considerations and require additional diagnostic testing or longer-duration treatment courses.^{5,6}

LEARNING OBJECTIVES

Upon completion of this program, the participant should be able to:

- Discuss the etiology of acute cystitis
- Describe the consequences of the increase in antimicrobial resistance on the management of acute cystitis in the pregnant and pediatric patient populations
- Determine the risk factors that influence the development and recurrence of acute cystitis in the pregnant and pediatric patients
- Identify the benefits and disadvantages of both traditional and newer antimicrobial agents in the pregnant and pediatric patient
- Review the latest pharmacologic/nonpharmacologic strategies for prevention
- Understand the unique management strategies relative to the pregnant and pediatric patient populations

OVERVIEW—The Pregnant Patient

UTIs are a common medical complication during pregnancy.⁷ From 0.3% to 1.3% of pregnant women develop acute cystitis,^{8,9} most frequently during the second trimester.¹⁰ From 5% to 10% of pregnant women have ASB on screening in the first trimester.⁸ The prevalence of ASB is similar in nonpregnant and pregnant women, but ASB is associated with significant morbidity among pregnant women and is benign in nonpregnant women.^{11,12} If left untreated, 20% to 30% of women with ASB will eventually develop pyelonephritis. Pregnant women with acute pyelonephritis are at an increased risk for premature delivery. Treatment of ASB reduces this risk by 80% to 90%.⁸ Consequently, any ASB or UTI occurring during pregnancy requires treatment.

The pathogenesis of UTI in pregnant patients differs from that of otherwise healthy adult populations. Pregnant women are at increased risk for UTIs as the result of anatomic and physiologic alterations associated with pregnancy (Table 1).

The etiology of UTI during pregnancy is similar to that of nonpregnant women. *Escherichia coli* is the most common uropathogen (Table 2, page 2)⁷, with *Klebsiella* spp, *Enterobacter* spp, *Proteus mirabilis*, *Staphylococcus saprophyticus*, and group B beta hemolytic streptococcus much less frequent.⁹ *Gardnerella vaginalis* and *Ureaplasma urealyticum* may be isolated but have not been shown to have a significant pathogenic role.⁷

Management of UTI during pregnancy must consider efficacy as well as safety for both the mother and fetus. Resistance of infecting organisms is

TABLE 1
PHYSIOLOGIC AND ANATOMIC CHANGES
DURING PREGNANCY^{8,24,25,37}

- | | |
|---|---|
| • Ureteral dilatation | • Ureteral obstruction with pressure of fetal head at pelvic brim |
| • Change in bladder position | • Increased glomerular filtration rate |
| • Decreased bladder and ureteral tone | • Increased urine pH |
| • Increased urinary stasis | • Increased urinary content of amino acids |
| • Increased plasma volume | |
| • Increased bladder volume | |
| • Increased prevalence of vesicoureteral reflux | |

TABLE 2
MOST FREQUENT UROPATHOGENS CAUSING UTI & ASB ISOLATED IN PREGNANT WOMEN⁹

Pathogen	Frequency
<i>Escherichia coli</i>	86%
<i>Proteus mirabilis</i>	4%
<i>Klebsiella</i> spp	4%
<i>Enterobacter</i> spp	3%
<i>Staphylococcus saprophyticus</i>	2%
Group B beta hemolytic streptococcus	1%

also a consideration as well. Therapeutic options include antimicrobial agents with US Food and Drug Administration (FDA) pregnancy risk categorization of A or B and Hale's Lactation Risk Categories of L1 or L2 (Table 3). Some common antimicrobial agents are not indicated or recommended for use for pregnant patients because of the potential for teratogenic or other toxic effects (Table 4). One common rule of thumb is that any drug that can be administered to a neonate is also safe to use during breastfeeding.¹³

Several of the agents previously used as first-line empiric therapy are now encountering increased resistance in *E coli* and, perhaps, should no longer be used empirically. For pregnant women, the traditional first-line agents whose empiric use should be questioned are ampicillin and amoxicillin as up to one third of *E coli* isolated from the general population are resistant to ampicillin.⁶ In addition, significant increases in resistance rates of common uropathogens to TMP/SMX also limit its empiric use by nonpregnant adults, especially in geographic areas where the known resistance level to TMP/SMX is >10% to 20%.^{4,14,15} In general, susceptibility testing should be performed in all pregnant patients to ensure effective treatment.

Recently, research has demonstrated an elevated risk of neural-tube defects, cardiovascular defects, oral clefts, and urinary tract defects in infants born to women who had used folic acid antagonists, including TMP, during the first trimester of pregnancy.¹⁶ Multivitamin supplementation that includes folic acid may ameliorate the risk, but the use of folate antagonists, such as TMP and SMX, should be avoided, if possible, during the first trimester of pregnancy. The potential for exacerbation of newborn hyperbilirubinemia also limits the use of sulfonamides close to term.⁶

Fluoroquinolones such as norfloxacin, ciprofloxacin, levofloxacin, and gatifloxacin are contraindicated for pregnant women because of the theoretic

potential for impairment of cartilage development in the fetus.¹⁷⁻¹⁹ However, a small Canadian study found no evidence of musculoskeletal problems or congenital malformations of infants born to 38 women who received norfloxacin or ciprofloxacin for UTI during the first trimester. The authors recommended additional follow-up and magnetic resonance imaging of the joints in these infants.²⁰ Concerns about the abortifacient effects of fluoroquinolone agents when administered at high doses and risks of congenital malformations have also been raised.^{17,19,21} Fluoroquinolones are classified by the Food and Drug Administration as pregnancy category C pending well-controlled clinical studies to document safety. Clinicians are advised to refrain from using fluoroquinolones in pregnant women unless the potential benefit is significantly greater than the potential risks to the fetus.¹⁸

Nitrofurantoin is an antimicrobial which has remained effective for nearly 50 years for treatment of acute cystitis. It is a urospecific agent with indications limited to the management of acute cystitis for susceptible uropathogens. Bacteriologic cure with a 7-day regimen remains high (usually 85% to 90%),²² and resistance rates to common uropathogens have remained low (<2%) despite 50 years of use. The failure of resistance to emerge despite prolonged use may, in part, be attributed to multiple mechanisms and sites of action.¹⁵

Nitrofurantoin is an effective and nontoxic regimen, and while it has been given in regimens of <3 days, most experience in pregnancy is with a 7-day course.⁷ Rarely, nitrofurantoin has been associated with hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency.⁷ Because of its urospecific qualities and safety, it is an appropriate option for pregnant patients with acute cystitis. Nitrofurantoin is also a first-line choice for prophylaxis of acute uncomplicated urinary infection. Prolonged prophylactic use is safe and not associated with the development of resistance.²³ It has also been recommended for prophylaxis in pregnant women.

Fosfomycin tromethamine single-dose therapy (SDT) is a relatively recent addition to the UTI therapeutic armamentarium in North America. There are limited published clinical trials describing the efficacy or safety of fosfomycin SDT in either the general population or in specific subpopulations.²⁴ This agent crosses the placental barrier, but it is not known if it is excreted in breast milk. As the concentrations of fosfomycin in breast milk are unknown, it is not indicated for use by a breastfeeding mother. Fosfomycin is effective during pregnancy²⁵ and is classified as pregnancy category B. The FDA recommends its use only if the benefits clearly outweigh the risks to the fetus. Finally, fosfomycin is not recommended for use in complicated infections or for prophylaxis due to the rapid rise of resistance with longer duration of use.²⁶

TABLE 3
FDA PREGNANCY RISK CATEGORIES⁶⁹

Category A	Category B	Category C	Category D	Category X
Well-controlled human studies=no fetal risk in 1st trimester. No evidence of risk in 2nd, 3rd, trimesters. Risk to fetus appears remote.	Animal studies do not demonstrate fetal risk. No controlled studies in humans or animal studies show AEs but not demonstrated in humans.	No controlled study in humans available. Animals reveal adverse fetal effects.	Positive evidence of human fetal risk. Use in pregnant woman occasionally acceptable despite risk.	Animal/human studies demonstrate fetal abnormality. Evidence of fetal risk based on human study. No indication in pregnancy.

LACTATION RISK CATEGORY⁷⁰

L1: Safest, controlled study fails to demonstrate risk	L4: Hazardous, positive evidence of risk, may be used if maternal life-threatening situation
L2: Safer, limited number of woman studies without risk	L5: Contraindicated, significant, and documented risk
L3: Moderately safe, no controlled study or controlled study shows minimal, nonlife-threatening risk	

TABLE 4
UTI ANTIMICROBIALS AND PREGNANCY^{6,71}

Antimicrobial Agent	Benefits	Concerns
Ampicillin, amoxicillin [related penicillins]*	<ul style="list-style-type: none"> Traditional drug of choice Class B; L1/L2 	<ul style="list-style-type: none"> <i>E coli</i> resistance (20%-60%)
Cephalosporins	<ul style="list-style-type: none"> Well-tolerated Adequate response rate Class B; L1/L2 	<ul style="list-style-type: none"> Candidal vaginitis
Sulfonamides*		<ul style="list-style-type: none"> Class C (1st/2nd trimester); L3 Class D (near term) Increased risk kernicterus 3rd trimester Increased rate <i>E coli</i> resistance Risk of toxicity in newborns Significant levels persist in neonate
Trimethoprim*		<ul style="list-style-type: none"> Class C; L3 Class D (1st trimester) Increased risk of congenital deformities Increased rate <i>E coli</i> resistance Folate antagonist Teratogenic/embryotoxic in animals
Nitrofurantoin (macrocrystals or monohydrate/macrocrystals)	<ul style="list-style-type: none"> Safe, effective Urospecific Class B; L1/L2 	<ul style="list-style-type: none"> Avoid if G6PD deficiency and close to delivery
Fluoroquinolones		<ul style="list-style-type: none"> Contraindicated Class C; L3 May impair cartilage development
Fosfomycin	<ul style="list-style-type: none"> Class B 	<ul style="list-style-type: none"> Unknown if excreted in breast milk (unknown concentrations) Limited experience Readily crosses placental barrier
Tetracycline		<ul style="list-style-type: none"> Contraindicated Class D May impair bone and tooth development

*The American College of Obstetricians and Gynecologists (ACOG) recommends use only if sensitivities are available.

OVERVIEW—The Pediatric Patient

Diagnosis and management of UTI in neonatal and pediatric populations is also important. Approximately 3%²⁷ to 8%²⁸ of prepubertal girls and 1% of prepubertal boys experience at least one UTI. UTI is more prevalent among boys throughout the first year of life, after which UTI is significantly more prevalent among females at every age.²⁹ UTI may be an indication of underlying genitourinary abnormalities in a prepubertal child. Congenital abnormalities are of particular concern. Abnormalities may include posterior urethral valves, obstruction, dysplasia, hydronephrosis, vesicoureteral reflux (VUR), or renal scarring.³⁰

The pathogenesis of UTI in neonates (through 12 weeks of age) is thought to be usually secondary to a hematogenous seeding associated with bacteremia, whereas UTIs occurring after 3 months of age are usually the result of an ascending infection from the urethra, similar to older children and adults.

E coli is also isolated from about 80% of UTIs in children.³¹ Children with recurrent UTI (RUTI) or receiving antibiotic prophylaxis have a greater incidence of UTI due to *Proteus* spp, *Klebsiella* spp, and *Enterobacter* spp.³¹

Some antimicrobials are not indicated for use in pediatric populations due to concerns regarding musculoskeletal development (Table 5). In addition, emerging resistance of *E coli* to ampicillin makes ampicillin and amoxicillin less effective than alternative agents for empiric therapy.⁵ Fluoroquinolones are contraindicated for pediatric patients because of the potential for cartilage toxicity and arthropathy.^{17,18} Clinical evidence suggests, however, that fluoroquinolones may be safe and effective agents for selected specific infections and diseases in pediatric populations, including complicated UTI when no other alternatives are available.^{32,33}

Nitrofurantoin is effective in treating lower UTIs in children, and may be an appropriate alternative to TMP/SMX^{34,35} in nonfebrile children over 1 month of age.³⁶ Nitrofurantoin should not be used to treat UTI in febrile infants and young children in whom renal involvement is likely, as it does not reach therapeutic levels in the bloodstream or kidneys.⁵ Nitrofurantoin is recommended for use as prophylaxis in children (1 to 2 mg/kg as single daily dose) by the AAP.

Finally, the safety and efficacy of fosfomycin in patients under 12 years of age is not yet established. Data regarding the use of fosfomycin in children are limited and, therefore, it is not recommended for use in the pediatric population.

The 4 cases presented in this newsletter highlight the challenges facing clinicians who diagnose and manage UTI in pregnant women or pediatric patients. The cases include:

- A 27-year-old pregnant woman with symptomatic UTI during the second trimester. What is the impact of UTI on the pregnancy and the developing fetus? What antibiotics are safe and effective? What is the impact of resistance on antimicrobial selection?
- A 33-year-old pregnant patient with recurrent ASB at 32 weeks gestation. What are the screening recommendations? What are the risks of

TABLE 5
ORAL ANTIMICROBIALS FOR EMPIRIC TREATMENT OF PEDIATRIC UTI*

Regimen

TMP/SMX** 6-12 mg TMP, 30-60 mg SMX/kg body weight/day bid
 Amoxicillin** 20-40 mg/kg bodyweight/day in 3 doses
 Sulfisoxazole** 120-150 mg/kg body weight/day in 4 doses
 Nitrofurantoin† 5-7 mg/kg body weight/day in 4 doses
 Amoxicillin/clavulanate** 45 mg/kg body weight/day in 2 doses
 Cephalexin 50-100 mg/kg body weight/day in 4 doses

Treatment Duration

Cystitis treatment duration: [at least] 3 to 4 days
 Pyelonephritis treatment duration: 7 to 14 days

* Fluoroquinolones not approved for use in children <18 years of age

** Concerns over increasing resistance

† Not for use in complicated UTI/pyelonephritis

not treating ASB versus antimicrobial treatment? What are the American College of Obstetricians and Gynecologists (ACOG) guidelines for long-term suppressive therapy? Any effect on breastfeeding?

- An 11-month-old male with unexplained fever. Should you test for UTI? How to collect the urine specimen? Any potential medical consequences of UTI in this age group? Any underlying urinary tract abnormalities? What are the American Academy of Pediatrics (AAP) guidelines for diagnosis and management?
- A 3½-year-old female in a day-care setting with recurrent UTIs. Any underlying anatomic abnormality? What diagnostic measures are indicated? How to manage acute infection? Prophylaxis? Effect of day-care setting on resistance? Association between renal scarring and RUTI?

CASE 1: SYMPTOMATIC AUC DURING SECOND TRIMESTER

This case describes a 27-year-old woman in her second trimester of pregnancy. She has a history of intermittent UTIs prior to her pregnancy, and presents to her obstetrician with dysuria and urinary urgency and frequency. Her initial prenatal screening urine culture was negative. Acute cystitis was diagnosed based upon clinical presentation and urinalysis. Considerations for management include the potential for antimicrobial resistance and follow-up after treatment; posttreatment monthly screening throughout the remainder of the pregnancy was recommended.

Clinical Presentation and History

A 27-year-old woman in the second trimester of her first pregnancy (19 weeks gestation) presented to her obstetrician with dysuria, urgency, and urinary frequency. She reported no chills, fever, or flank pain, and there was no vaginal discharge or odor upon examination. She had a history of intermittent UTIs after she first became sexually active at age 20, all of which responded promptly to antibiotic treatment. ACOG recommends that each obstetric patient undergo a urine culture at the initial prenatal visit (Table 6).⁶ This patient's initial urine culture was negative, and subsequent obstetric visits have been normal. Her current symptoms were similar to those experienced with her previous episodes of urinary infection.

Diagnostic Considerations

As with nonpregnant adult women, dysuria, urinary frequency and urgency, hematuria, and suprapubic discomfort without upper urinary tract symptoms (fever, costovertebral angle tenderness, and flank pain) are clinically consistent with cystitis.⁹ These symptoms may occur without urinary infection in the pregnant woman, so infection must be confirmed with microbiologic testing. Based on the clinical presentation, a urine dipstick was performed on a clean-catch midstream sample^{7,8} and was positive for pyuria and nitrates. The urine culture subsequently grew *E coli*—≥10⁵ cfu/mL.

Management Issues

Management of AUC during pregnancy is generally similar to that of AUC in the nonpregnant adult woman, but treatment during pregnancy must consider safety of the antimicrobial agent for both the mother and fetus. Empiric antimicrobial therapy may be initiated prior to culture results, but should be reviewed once susceptibility results are available. ACOG recommends the use of a minimum of 3-day treatment with as narrow spectrum an agent as possible to minimize the risk of resistance.⁶ Despite the ACOG recommendations for 3-day therapy, longer durations of 5 to 7 days are suggested by some authors.^{9,37} Whatever treatment duration is selected, a follow-up culture—approximately 7 days after treatment completion to document successful eradication—is recommended.⁶

Commonly used antibiotic agents for acute cystitis during pregnancy include nitrofurantoin, cephalexin, and amoxicillin. ACOG recommends TMP/SMX, nitrofurantoin (macrocrystals or monohydrate/macrocrystals), or cephalexin. Fluoroquinolones and tetracyclines are contraindicated during

pregnancy. Increasing rates of *E coli* resistance to TMP/SMX³⁸⁻⁴⁰ and amoxicillin⁶ now limit empiric use of these agents. There are concerns of increased neonatal jaundice and kernicterus in newborns (particularly preterm infants) with the maternal use of sulfonamides close to term,¹³ and congenital defects with trimethoprim use during the first trimester.¹⁶ Nitrofurantoin should be avoided in women with hereditary glucose-6-phosphate dehydrogenase (G6PD) deficiency and may not be appropriate for use close to term because of a theoretic risk of hemolysis with fetal hemoglobin.⁶

In general, treatment of symptomatic UTI during pregnancy should be empiric and tailored to culture/sensitivity results once available. The most appropriate antimicrobial options for this second-trimester patient include nitrofurantoin, cephalexin, or TMP/SMX. These drugs are considered safe and effective for UTI management during the second trimester. Increasing antimicrobial resistance to TMP/SMX may make this agent less attractive for empiric therapy, depending upon the patient's geographic residence. Up to 50% of women with cystitis caused by a resistant organism will fail therapy.^{14,41} According to the IDSA Guidelines, β-lactams as a group are less effective in treating cystitis than are TMP/SMX, TMP alone, or the fluoroquinolones.⁴ Therefore, nitrofurantoin would be an appropriate antibiotic selection for this patient.

Case Conclusion and Commentary

Following a diagnosis of acute cystitis at any time during pregnancy, monthly follow-up cultures to identify bacteriuria throughout the remainder of the pregnancy are recommended. Approximately 18% of patients with acute cystitis develop ASB later in the pregnancy.⁹ In addition, women with ASB during pregnancy are more likely to deliver low birth-weight babies and preterm low birth-weight infants.⁴² If there are recurrent episodes of bacteriuria or cystitis, long-term daily suppressive treatment with nitrofurantoin (50 to 100 mg/night) or a cephalosporin is recommended throughout the course of pregnancy.^{6,43}

CASE 2: ASYMPTOMATIC BACTERIURIA DURING PREGNANCY

This case describes a 33-year-old woman in her 32nd week of gestation. She has recurrent ASB originally identified and treated following the first trimester screening. She also reported being treated for a UTI when she was in college. The clinical challenge is identification and treatment of ASB during pregnancy. What are the benefits versus risks of treatment? Of nontreatment? Risks for breastfeeding?

Clinical Presentation and History

A 33-year-old woman with a remote prior history of UTI has ASB at her first 2 initial screenings (at which times she was treated with an antibiotic) and again at her third trimester screening. She reports no symptoms of UTI,

TABLE 6
UTI SCREENING RECOMMENDATIONS DURING PREGNANCY

- ACOG⁶
 - Obtain urine culture at first prenatal visit
 - Repeat urine culture during 3rd trimester
- US Preventative Services Task Force⁴⁸
 - Obtain urine culture between 12 to 16 weeks gestation ("A" recommendation)
- Following a diagnosis of ASB or UTI at anytime,
 - A follow-up culture should be obtained 7 to 10 days after treatment completion⁹
 - Monthly follow-up cultures until delivery to document sterile urine

specifically no dysuria, urinary urgency or frequency, and no fever, chills, or flank pain. Her history of prior UTI in her 20s increases the likelihood she will have bacteriuria during pregnancy.⁴⁴

Diagnostic Considerations

ACOG guidelines state all pregnant women should be screened for ASB during the initial prenatal visit, and again during the third trimester (Table 6).^{6,44} Following a diagnosis of ASB, monthly follow-up cultures to verify sterile urine are recommended. Screening for and treatment of ASB during pregnancy minimizes the subsequent incidence of pyelonephritis in late pregnancy.⁴⁵ A single clean-catch midstream urine specimen is recommended to diagnose ASB; obtaining a second specimen following an initial positive increases the reliability of identification of ASB. Catheterization to collect urine culture is not indicated.

ACOG recommends that women who test positive for nitrites by a dipstick technique should have the diagnosis confirmed by culture. However, studies suggest as many as 50% of women with ASB in pregnancy will have a negative dipstick screening test.^{46,47} A US Preventive Services Task Force report recommends against the use of urine dipstick (nitrite and leukocyte-esterase) tests, and that urine culture is necessary for screening.^{48,49}

As with this patient, women with ASB in early pregnancy frequently have recurrent bacteriuria later in pregnancy and are at increased risk of developing pyelonephritis.⁴⁹ Only 1% to 2% of women with sterile urine at the initial prenatal screening culture will subsequently develop pyelonephritis later in pregnancy.^{9,49}

Management Issues

ASB rarely requires antimicrobial therapy in the nonpregnant adult woman. Nontreatment of ASB in the pregnant woman may have significant negative effects for both the mother and fetus/newborn. Approximately 5% to 10% of pregnant women have ASB⁹; if untreated, 20% to 40% will develop acute symptomatic infection⁷ (Table 7) and 20% to 30% will develop pyelonephritis.⁹ Untreated ASB has also been associated with preterm delivery,⁵⁰ and increased risk of delivering low birth-weight infants.^{42,50,51}

Management of bacteriuria during pregnancy is similar to management of cystitis during pregnancy (Table 8). Recommended antimicrobials include TMP/SMX, amoxicillin, nitrofurantoin, and cephalosporins.^{6,49} All appear equally efficacious.⁹ Regardless of the agent selected, 20% to 30% of women will have recurrent ASB following antimicrobial therapy during the remainder of the pregnancy.⁹ Treatment of ASB should be based on culture/susceptibility results as increasing resistance of *E coli* to TMP/SMX and high resistance rates to ampicillin limit their empiric use. Sulfa drugs are not recommended close to term. Consequently, the best options for antimicrobial management for this patient include nitrofurantoin or a cephalosporin. Nitrofurantoin is a urospecific agent that is safe and effective for the management of acute cystitis and ASB during pregnancy.⁵² It

TABLE 7

ADVERSE OUTCOMES ASSOCIATED WITH UNTREATED ASB AND/OR SYMPTOMATIC ACUTE CYSTITIS IN PREGNANCY

- Pyelonephritis^{7,9}
- Possible anemia⁷
- Preterm delivery⁷
- Possible hypertension in mothers⁷
- Low birth weight⁷
- Fetal death in infants⁷
- Intrauterine growth retardation⁷
- Possible mental retardation/developmental delays in infants⁷²

TABLE 8

MANAGEMENT OF ASB DURING PREGNANCY

- Prenatal screening – clean-catch midstream specimen
 - Treatment indicated: $\geq 100,000$ CFU/mL of single organism
- Antimicrobial options for treatment
 - TMP/SMX
 - TMP – avoid in 1st trimester
 - SMX – avoid close to term
 - Consider local prevalence of resistance in *E coli*
 - Ampicillin/amoxicillin
 - High rates of resistance
 - Nitrofurantoin
 - Avoid during labor and delivery
 - Most likely to have in vitro activity against common uropathogens
 - Option for prophylaxis
 - Cephalosporins
 - Possible increased vulvovaginal candidiasis
 - Option for prophylaxis
- Follow-up culture (7 to 10 days later)
- Monthly urine culture if ASB/UTI detected at any time during pregnancy
- Antibiotic prophylaxis if recurrent ASB

should be avoided during labor and delivery and for the few women with known G6PD deficiency. Unlike TMP/SMX and ampicillin, resistance of *E coli* to nitrofurantoin remains low at $<2\%$.^{15,24}

Duration of antibiotic treatment for ASB is controversial.³⁷ Many clinicians utilize 3 to 5 day regimens,⁵³ while others recommend longer regimens (7 to 10 days). Regardless of the regimen selected, a follow-up culture should be obtained 7 to 10 days after treatment completion to document sterile urine. Women diagnosed at any time during pregnancy with ASB or symptomatic UTI should have monthly urine cultures until delivery to ensure continuing sterility. Women with recurrent bacteriuria require retreatment based upon susceptibility testing, followed by continued prophylactic therapy if bacteriuria recurs. Options include nitrofurantoin (50 to 100 mg/ohs) or cephalexin (250 to 500 mg ohs) until delivery.^{7,24,54}

Case Conclusions and Commentary

Management of ASB during pregnancy is similar to that of symptomatic infection. It may be challenging for the clinician to convince a woman with ASB to adhere to a regimen of antibiotics during pregnancy. Up to 25% of women diagnosed with UTI during pregnancy do not fill their antibiotic prescriptions.⁵⁵ Women with untreated ASB are at an elevated risk of preterm delivery and low birth-weight infants, preeclampsia, chronic renal diseases, and postpartum endometritis.^{24,49} Many women are also concerned about antibiotic use during breastfeeding. Almost all drugs are excreted into breast milk. In general, any drug that can be administered to a neonate is safe to use during breastfeeding.¹³ The clinician must address any patient concerns regarding the safety of the medication for both mother and fetus¹³ during pregnancy and/or breastfeeding, and balance these against the potential medical sequelae and risks of nontreatment. Lastly, treatment of ASB should be based on culture/susceptibility results.

CASE 3: ACUTE CYSTITIS IN 11-MONTH-OLD MALE

This case discusses an 11-month-old premature infant presenting to his pediatrician with unexplained fever and appearing to his parents as “ill.” His fever and general status suggested a diagnosis of UTI. Hospitalization with parenteral antibiotics was indicated, and imaging studies identified an underlying anatomic abnormality requiring surgical intervention.

Clinical Presentation and History

An 11-month-old infant was brought to the pediatrician with unexplained fever (38.5°C). His parents described him as lethargic and “appearing ill.” He appeared to cry upon urination and there was a foul smell associated with the urine, both findings associated with UTI.⁵ He had been born 3½ weeks prematurely, which also increases the risk of UTI.⁵

Diagnostic Considerations

The first diagnostic challenge was to ascertain the cause for the unexplained fever. The classic localizing symptoms of UTI—dysuria and urinary frequency/urgency—are rarely present in an infant⁵⁶; UTI symptoms in infants are more likely systemic (fever, lethargy, vomiting, anorexia).⁵⁷ Other potential sources for unexplained fever, such as otitis media, do not necessarily rule out concomitant UTI. It has been estimated that about 7.5% of febrile infants have UTI.⁵⁸ Recent guidelines from the American Academy of Pediatrics (AAP) recommend suspicion of UTI in all infants or young children (aged 2 months to 2 years) with unexplained fever (Table 9).⁵ Clinical assessment must differentiate whether the UTI is lower (cystitis) or upper tract (pyelonephritis). High fevers ($\geq 39^{\circ}\text{C}$) are often a marker for pyelonephritis, whereas absent or low grade fevers ($\leq 38^{\circ}\text{C}$) are more suggestive of acute cystitis. Additional diagnostic tests, including white blood cell count, C-reactive protein, or sedimentation rate, may aid in differential diagnosis, as elevated results are more common in pyelonephritis. If pyelonephritis is suspected, imaging studies may also prove useful.⁵

The AAP guidelines state it is cost effective to pursue a diagnosis of UTI in young girls, circumcised boys ≤ 1 year, and uncircumcised boys < 1 year through invasive means (suprapubic aspiration [SPA], transurethral catheterization).⁵ In nontilet-trained children ill enough to warrant immediate antibiotic therapy, a urine specimen should be obtained via SPA or in-and-out bladder catheterization. A catheterized specimen is the most reliable method to sample bladder urine in nontilet-trained children.⁵⁹ A culture-negative urine bag sample is reliable, but there is a high rate (16%) of false positive results, particularly among uncircumcised males and newborn females, due to contamination by periurethral flora.⁵⁹ Thus, use of a bag-collected urine specimen is insufficient to diagnose UTI.

Nearly 50% of infants diagnosed with a UTI under 1 year of age have an underlying urinary tract abnormality—most commonly, vesicoureteral reflux (VUR).³⁰ There is also an increased risk of acute renal injury with UTI during early childhood.⁵ Thus, a sonogram should be performed on all infants and young children with fever and their first documented UTI. Renal ultrasound is recommended to define the renal structure and identify dilatation of the collecting system, and cystography [either with voiding cystourethrography (VCRG) or radionuclide cystography (RNC)] is used to define and grade vesicoureteral reflux. The goals of imaging studies are to help identify management strategies to prevent renal scarring in the growing kidney by correcting UT abnormalities, decreasing the frequency of recurrent UTI, and reducing the risk of progression to pyelonephritis.^{5,60} For children with suspected pyelonephritis, dimercaptosuccinic acid cortical scintigraphy (DMSA scan) is more sensitive than ultrasonography in detecting renal involvement, and is recommended.⁶¹

For this patient, the clinical presentation led to blood and urine cultures being obtained. *Proteus mirabilis* was cultured, and white blood cell count was elevated in the urine (> 5 WBC/high power field). Imaging studies identified bilateral hydronephrosis on ultrasound and posterior urethral valves were found on cystography. Subjective assessment of toxicity and dehydration led to hospitalization and parenteral antibiotic therapy. A pediatric urologist was consulted.

TABLE 9

AMERICAN ACADEMY OF PEDIATRICS URINARY TRACT INFECTIONS (UTI) TREATMENT GUIDELINES: RECOMMENDATIONS⁵

- Suspect UTI with unexplained fever in children aged 2 months to 2 years
- Assess the degree of toxicity, dehydration, and the ability to retain oral intake
- Obtain a urine specimen by either suprapubic aspiration (SPA) or catheterization if the child is ill enough to warrant immediate presumptive antibiotic usage. A “bagged” specimen is not sufficient
- A urine specimen for urinalysis and culture can be obtained by SPA, catheterization, or another convenient means when the child is not judged ill enough for immediate presumptive antibacterial therapy for UTI
- Diagnosis of pediatric UTI requires urine culture
- If the child is “toxic,” dehydrated, or unable to retain fluids, initial antibacterial therapy should be given parenterally and hospitalization considered
- If the child is not judged ill enough to need immediate presumptive antibacterial therapy, and has a urinalysis suggesting or culture confirming UTI, antibiotic therapy (parenteral or oral) should be started when culture results are available
- If there is no clinical response within 2 days of antibiotic therapy, another urine specimen should be obtained for culture
- Children whose treatment was initially given parenterally should complete 7 to 14 days of total antimicrobial treatment (oral + parenteral)
- Children should continue to receive antibiotics in therapeutic or prophylactic dosage until imaging studies are complete
- Children who do not have an adequate clinical response within 2 days of initiating antimicrobial therapy should have prompt RBUS and VCUG. Children with a satisfactory clinical response should have RBUS and VCUG (RNC) at the earliest convenient time. Boys must have a standard fluoroscopic VCUG

RBUS = renal and bladder ultrasound; RNC = radionuclide cystography; SPA = suprapubic aspiration; VCUG = voiding cystourethrogram.

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Management Considerations

The AAP practice parameters for UTI focus on treating the acute infection, preventing urosepsis, and minimizing the likelihood of renal damage.⁵ This patient required immediate hospitalization and intravenous antimicrobial therapy. Appropriate antibiotics included an aminoglycoside, with or without ampicillin, or a third-generation cephalosporin. TMP/SMX or amoxicillin may be indicated for subsequent oral therapy if the organism is susceptible, but nitrofurantoin is not recommended because of possible renal involvement.

Once the infant was stabilized and clinically responding to the IV medications, parenteral therapy was switched to an oral antibiotic (5 mg TMP/25 mg SMX/kg/2 x week) to complete 14 days of treatment. If he had not responded within 48 hours to the initial treatment, reevaluation would have been necessary, including culture of a second urine specimen. Subsequent antimicrobial prophylaxis was continued for 6 months after urologic surgery to correct the posterior urethral valves.

Case Conclusions and Commentary

UTI in an infant (2 months through 2 years) is often the first sign of a urinary tract abnormality. Prompt diagnosis and treatment will minimize the risk of severe medical sequelae that can include pyelonephritis, urosepsis, and renal damage. The strongest predictors of renal damage and, therefore, a poor prognosis include delays in diagnosis and treatment and anatomic obstruction.⁶² Higher grade VUR (grades 3 to 5) increases the risk of recurrence.⁶³ With VUR, recurrent ASB is often detected upon follow-up examination, frequently within 6 months of the index infection. Thus, antibiotic prophylaxis is recommended for at least 6 months.

CASE 4: ACUTE CYSTITIS IN A 3-YEAR-OLD FEMALE

This case discusses a 3½-year-old otherwise healthy female with recurrent UTI cared for in a day-care setting. Her symptoms did not warrant hospitalization and the UTI was managed with oral antibiotics, with prophylactic nitrofurantoin prescribed for continuing therapy.

Clinical Presentation and History

A 3½-year-old girl was brought to her pediatrician with low-grade fever (37.8°C) and apparent discomfort upon urination. She did not appear ill and was not vomiting, but did have abdominal tenderness. Her limited verbal skills limited her ability to describe or localize pain. This was her third UTI since entering this day-care setting 10 months earlier; imaging studies had not been ordered with her prior UTIs.

Diagnostic Considerations

This child was not ill enough to warrant catheterization or suprapubic aspiration (SPA). In a toilet-trained child, a voided midstream urine culture is the preferred technique for urine collection. It is not necessary to cleanse the urethral meatus prior to specimen collection. If the child is instructed to sit in a reverse position on the toilet seat (which naturally separates the labia from the urethral meatus), a specimen is more easily collected.

Children who have their first UTI after age 2 are less likely than younger children to have anatomic abnormalities underlying the UTI. However, recurrent UTIs indicate the need for additional imaging studies. Imaging can be a radionuclide isotope cystogram (RNC), or a radiographic voiding cystourethrogram (VCUG), which better detects urethral or bladder wall anomalies.⁶⁴ A VCUG was ordered and the imaging was normal.

Management Considerations

Approximately 1% to 3% of girls aged 1 to 5 years will have a UTI,²⁹ and 30% with a normal genitourinary tract will have a recurrence, usually during the first few months following the first infection. From 60% to 70% of girls with one recurrence will have additional recurrences.²⁹

This patient did not appear ill, was not vomiting, and, through her parents, could comply with medical instructions. Clinical assessment did not suggest hospital admission or parenteral antibiotics were necessary. Management focused on oral antibiotics including TMP/SMX, amoxicillin, cephalexin, or nitrofurantoin. There is little information describing urinary *E coli* resistance rates in pediatric populations. Resistance is of concern because there are fewer antibiotic agents for use in the pediatric population, and prognosis is improved with prompt and effective treatment. The following 3 factors might increase the risk of TMP/SMX resistance: (1) child aged 2 to 6 years, (2) multiple inpatient hospitalizations, and (3) previous antimicrobial treatment for >4 weeks in the preceding 6 months.⁶⁵ This patient was between 2 and 6 years, attended day-care, and was previously treated with TMP/SMX. Sensitivity testing was performed and revealed *E coli* resistance to TMP/SMX. Nitrofurantoin was prescribed. Pediatric patients with recurrent infection, including those with a diagnosed UT abnormality, should also be considered for antimicrobial prophylaxis.⁶⁵

Treatment durations for pediatric patients remain controversial. Three-day courses may be as effective as 7 to 14 day courses,³⁴ but a recent

meta-analysis suggested longer courses of therapy had fewer treatment failures.³⁵ Thus, some practitioners prefer 5 to 7 day therapy.

Day-care settings facilitate the emergence of antibiotic-resistant bacteria. Factors which contribute to this include close contact among children; poor personal hygienic practices among children, and widespread use of antibiotics.⁶⁶⁻⁶⁸ Stool samples from diapered children in 4 day-care settings found a 30% prevalence of fecal colonization with multiresistant *E coli* (TMP, sulfisoxazole, streptomycin, and ampicillin resistance) compared to 6% in diapered children cared for in home settings.⁶⁷ Transmission and carriage of TMP-resistant strains in the day-care setting was documented for up to 6 months,⁶⁷ and transmission of the resistant strains to family members was common.⁶⁶ Day-care centers are now believed to be an important community reservoir of antibiotic-resistant *E coli*; antibiotic selection must therefore take these findings into consideration.

Case Conclusions and Commentary

This child was not acutely ill and did not require hospitalization. However, as with infants and younger children, older children (>2 years) with recurrent UTI should undergo an imaging evaluation. Prophylaxis may be considered for children with recurrent UTI. Of the agents available for long-term prophylaxis, nitrofurantoin and TMP/SMX are the most likely choice because of their long-term safety record. The AAP guidelines do not recommend the use of β -lactams for prophylaxis. Concerns regarding the high rate of antimicrobial resistance in some areas of the United States to TMP/SMX may limit the efficacy of this agent.

Diagnosis of UTI in toddlers can be challenging due to their limited verbal skills, and inability to localize pain. Toilet-trained toddlers may not require catheterization or SPA for urine specimen collection; an appropriately collected voided midstream urine culture may be obtained. Of particular concern with this patient was her attendance at a day-care setting, which increased her risk for antibiotic-resistant strains. Management selection focused on nitrofurantoin due to its safety and efficacy in children, including a low level of *E coli* resistance.

CONCLUSIONS

Acute lower UTIs are common, but generally benign, infections in most populations. However, UTIs can have serious medical consequences in pregnant women and pediatric patients. Suspicion of UTI in either of these 2 populations requires additional diagnostic testing and may require longer treatment durations for cystitis. During pregnancy, both symptomatic UTI and asymptomatic bacteriuria require prompt diagnosis and antibiotic treatment to prevent pyelonephritis and its concomitant medical risks of preterm delivery and low birth-weight infants. ACOG recommends initial urine screening during the first prenatal visit with subsequent screening during the third trimester. Pregnant women diagnosed with ASB or UTI should subsequently receive monthly urine cultures with prophylaxis, if indicated, until delivery.

UTI during infancy or early childhood is associated with a higher likelihood of genitourinary abnormalities. Delayed diagnosis and treatment may result in renal scarring and other serious medical sequelae. AAP recommends imaging studies for all infants aged 2 months through 2 years with unexplained fever and a diagnosis of UTI.

The etiology of UTI is similar for pregnant women, pediatric patients, and the general population, with *E coli* the most prevalent uropathogens. Fluoroquinolones, tetracyclines, and fosfomycin are not considered appropriate for use for urinary infection in pregnant women or young children because of potential toxicities. Resistance of common uropathogens (particularly *E coli*) to ampicillin limits its use for empiric therapy, and increasing resistance to TMP/SMX may also limit use. For pregnant women or pediatric patients not requiring hospitalization and parenteral antibiotics, oral nitrofurantoin and, where susceptibility is known, β -lactams remain safe and effective empiric options for the acute management of UTI or ASB; these agents are also appropriate for prophylaxis.

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MANAGING ACUTE UNCOMPLICATED CYSTITIS IN WOMEN IN THE ERA OF ANTIBIOTIC RESISTANCE: A CASE-BASED APPROACH TO THE PREGNANT WOMAN AND THE PEDIATRIC POPULATION

CME Credit Information and Posttest Assessment

Course No. EN0303 **For Primary Care Physicians, Obstetrician/Gynecologists, Urologists, and Healthcare Professionals Who Treat Patients With Acute Cystitis**

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Washington School of Medicine and IMED Communications. The University of Washington School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Washington School of Medicine designates this educational activity for a maximum of 1.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

To apply for category 1 credit, you must:

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Verification of Hours

I certify that I spent _____ hours in this CME activity as indicated by my signature below.

Signature

Within 2 weeks following the receipt of this form, a transcript of your category 1 hour will be mailed to you. Credit hours for this newsletter may be obtained from April 2003 through April 2005.

POSTTEST ASSESSMENT: *Please circle the correct answer.*

1. Diagnosis of UTI in a pregnant woman requires:
 - a. Symptomatic presentation including dysuria and urinary frequency
 - b. Catheterized urine specimen
 - c. Single clean-catch midstream urine specimen with culture
 - d. All of the above
2. Which of the following antibiotics are indicated for use during the first trimester of pregnancy?
 - a. Fosfomycin
 - b. Ciprofloxacin
 - c. Trimethoprim
 - d. Nitrofurantoin
3. According to ACOG Guidelines, when should pregnant women be screened for ASB?
 - a. Initial prenatal visit and again at ~20 weeks
 - b. Initial prenatal visit and during the 3rd trimester
 - c. Between 12-16 weeks gestation
 - d. At every prenatal check
4. Recurrent ASB in pregnancy requires what management approach?
 - a. Hospitalization with parenteral antibiotics
 - b. Short-duration (3-5 days) treatment with TMP/SMX, amoxicillin, or nitrofurantoin
 - c. Prophylaxis with TMP/SMX or amoxicillin until delivery
 - d. Treatment of the recurrent episode followed by prophylaxis with nitrofurantoin or cephalexin until delivery
5. Untreated ASB during pregnancy can result in which of the following?
 - a. Pyelonephritis
 - b. Preterm delivery
 - c. Low birth weight infant
 - d. All of the above
6. According to the AAP Guidelines, how should a urine specimen be obtained for children not ill enough to warrant immediate presumptive antibiotics?
 - a. Suprapubic aspiration
 - b. Catheterization
 - c. Voided midstream urine culture
 - d. Any of the above
7. The AAP Guidelines recommend diagnostic imaging for:
 - a. Any child from age 2 months to 2 years diagnosed with UTI and unexplained fever
 - b. Any child through age 15 diagnosed with UTI who doesn't respond to antibiotics within 24 hours
 - c. Any child through age 5 diagnosed with RUTI
 - d. a & c
 - e. a & b
8. Children ill enough to warrant hospitalization often require parenteral treatment with which antibiotics?
 - a. Ampicillin (amoxicillin) + aminoglycoside
 - b. Nitrofurantoin
 - c. Nalidixic acid
 - d. Ciprofloxacin
9. Which of the following agents are recommended for long-term suppressive management of RUTI in pediatric patients by the AAP?
 - a. Ampicillin and amoxicillin
 - b. Nitrofurantoin
 - c. TMP/SMX
 - d. Ciprofloxacin
 - e. b & c
10. The most common uropathogen isolated in pregnant women and pediatric patients is:
 - a. Group B streptococcus
 - b. *Escherichia coli*
 - c. *Proteus mirabilis*
 - d. *Ureaplasma urealyticum*

EVALUATION FORM

We would appreciate your answers to the following questions in order to help us plan for future activities of this type.

1. How would you rate: Excellent Good Fair Poor
(please ✓)
 - a. Value of the topic ☐ ☐ ☐ ☐
 - b. Relevance to your practice ☐ ☐ ☐ ☐
 - c. Organization of newsletter ☐ ☐ ☐ ☐
 - d. Publication length ☐ ☐ ☐ ☐
 - e. Quality of information ☐ ☐ ☐ ☐
2. Were the goals and objectives clearly stated and achieved? ☐ Yes ☐ No
3. Will reading this newsletter change the way in which you manage patients? ☐ Yes ☐ No

Please be as specific as possible: _____

4. How do you prefer to receive continuing medical education information? (On a scale of 5 to 1, please score each of the following: 5=very useful; 3=somewhat useful; 1=don't use)
____ Newsletter ____ Journal Articles/Supplements
____ Videotape ____ Symposium/Conference
____ Audiotape/Audio CD ____ CD-ROM/Video
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____ Monograph
5. In your opinion, was the information in this newsletter biased toward any commercial product or service? ☐ Yes ☐ No

If yes, please comment: _____

6. Do you believe such materials, supported by educational grants from industry, are: 10 very appropriate/useful, 0 not appropriate/useful? _____

7. Additional comments and/or suggested topics for future CME activities: _____

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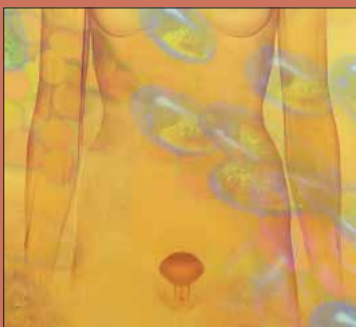
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